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Study of indicators of the immune status in HIV-infected patients with concurrent allergic pathology

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Abstract

Aim. To study the indicators of the immune status and manifestations of allergic diseases in HIV-infected patients in the Novgorod region.

Methods. We studied the data of HIV-infected patients living in the Novgorod region for the years 2000–2021. A total of 1020 cases of HIV infection were studied, in which 121 (12%) patients were diagnosed with allergic reactions. In patients with allergic manifestations, the human immunodeficiency virus type 1 ribonucleic acid content was measured by the polymerase chain reaction method, and the indicators of the immune status (the content of lymphocytes, eosinophils, basophils, the levels of $CD3^+$, $CD3^+CD4^+$, $CD3^+CD8^+$ cells, immunoregulatory index) were assessed. For statistical analysis, the Student's test (t) was used to assess the statistical significance of differences in immune status indicators, and the Pearson χ^2 test to assess the statistical significance of differences in allergic manifestations in patients with HIV.

Results. The subjects of the study were divided into 2 groups based on the levels of HIV viral load. Analysis of these groups using the Pearson χ^2 test showed a statistically significant ($p < 0.012$) correlation between high viral load and the development of drug hypersensitivity reaction in HIV-infected patients. The following etiology of allergic reactions was determined among the subjects: drug (59%), food (19%), pollen (5.7%), household (5.7%), chemical (1.9%), unspecified (6.7%). The study of the immune status in two groups did not reveal statistically significant differences ($p > 0.05$). The study of the immune status indicators in HIV-infected patients with drug hypersensitivity reactions and different levels of viral load revealed a significantly higher level of $CD3^+$ cells ($p < 0.003$) in patients with drug hypersensitivity reactions and detectable viral load.

Conclusion. The study revealed statistically significant differences in the immune status of HIV-infected patients with drug hypersensitivity reactions living in the Novgorod region compared with HIV-infected patients without drug allergies.

Keywords: HIV, allergy, immunology, drug hypersensitivity.

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Background. Human immunodeficiency virus (HIV) infection causes immunological alterations and leads to the development of allergic and other immunological diseases. A widespread prevalence of allergic rhinitis and non-infectious pulmonary complications was revealed among patients with HIV infection [1]. Additionally, frequent cases of drug allergy are reported in patients with HIV to a variety of groups of drugs, including antiretroviral drugs [2, 3].

Significant clinical, diagnostic, and therapeutic aspects of the pathophysiology of HIV infection must be considered in allergic diseases treatment. Understanding the interaction between HIV and hypersensitivity reactions can contribute to a more effective and correct treatment approach for patients with HIV infection.

HIV is the combined name of a group of RNA-containing viruses of the retrovirus family, which are genetically subdivided into two types, HIV-1 and HIV-2.

The first registered case of HIV infection dates back to 1981; however, data from the epidemiological and phylogenetic analysis indicate that the human population became susceptible to HIV as early as 1920–1940. [4]. Patients with HIV infection accounts for >38 million worldwide, including >1 million of the Russian Federation citizens [5]

The targets of HIV are $CD4^+$ lymphocytes (T-helpers), which are one of the most impor-

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tant cells of the human immune system. Affected T-helpers are eliminated from the blood of a patient with HIV infection in several ways. With a decreased level of $CD4^+$ cells of <300/μL, the body's immune response weakens to the extent that a person becomes susceptible to opportunistic infections and neoplastic processes [4].

Hyperimmunoglobulinemia E is an increased level of immunoglobulin E (IgE) of >2000 IU/ml. It is associated with conditions, such as allergic diseases, helminthic infestations, primary immunodeficiencies, and acquired immunodeficiency syndrome (AIDS) [6]. In HIV infection, increased IgE level is associated with impaired T-cell regulation, opportunistic diseases, and increased allergic manifestations. Elevated IgE levels are not a permanent diagnostic sign in the early stages of HIV infection. However, a study [7] revealed a persistent increase in IgE levels in the early stages of HIV-1 infection among a group of subjects. Impaired IgE synthesis in HIV infection may be due to cytokine profile changes of types 1 and 2 T-helpers (interferon γ and interleukin-4, respectively) as the disease progresses [8].

Among the people living with HIV, cases of allergic diseases, such as rhinitis, asthma, and skin eruptions characterized by atopic eczema, as well as drug hypersensitivity, and dermatitis, are known. There is an opinion that atopy in HIV infection is a consequence of genetic predisposition and environmental factors [9, 10]. Additionally, the hyperreactive response to exoallergens undergoes modifications that are associated with a Th2-mediated immune response. A clear relationship was established between the level of $CD8^+$ lymphocytes and the severity of symptoms of allergic diseases, in the pathophysiology of which $CD8^+$ cells play a significant role, including in the case of HIV infection [8].

Drug hypersensitivity in patients with HIV infection is 100 times more common than in HIV-negative people. The drugs that most often cause hypersensitivity reactions in patients with HIV infection include β-lactam antibiotics, anti-tuberculosis, antiretroviral, non-steroidal anti-inflammatory drugs, and anticonvulsants [3].

The drug allergy in HIV infection can be caused by the dysregulation of T and B lymphocytes of the immune system, as well as changes in drug metabolism, oxidative stress, cytokine profile, immune system over reactivation, and genetic factors. There is an opinion that drug hypersensitivity reactions in HIV infection cannot be attributed to any type of reaction according to the Gell and Coombs classification [3].

The development of allergic reactions in HIV infection has several possible mechanisms. Firstly, HIV viral particles can be a specific trigger for the development of allergies [9]; secondly, predictors of allergy in humans are known to be intrinsic in their genes [10–12]; and thirdly, allergosis can be a consequence of eosinophilic inflammation due to helminths [13].

The authors have already studied the issue of HIV infection and allergy comorbidity [14]. Additionally, drug hypersensitivity has been revealed to be more common among patients with HIV-infected than in the general population [15].

This study aimed to analyze the indicators of the immune status and manifestations of allergic diseases in patients with HIV infection in the Novgorod region from 2000 to 2021.

To achieve the stated goal, the following tasks were set:

1. Determine the prevalence of allergic diseases among patients with HIV infection living in Veliky Novgorod and the Novgorod region.

2. Identify the statistically significant differences between patients with HIV infection with and without drug allergic reactions in terms of the presence or absence of a detectable viral load.

Materials and methods. We analyzed the data of the primary documentation of patients (registration form No. 025-4/u) registered with the Novgorod Center for the Prevention and Control of AIDS and Infectious Diseases "Helper" (hereinafter referred to as the Center) from 2000 to 2021.

The data of the Center's patients who live in the Novgorod region was analyzed. The information about the history of allergies (allergic diseases and drug reactions), according to oral information provided by the patients and examination results by an allergist, was considered. The data of laboratory studies were analyzed, including the molecular biological study of blood plasma for the quantitative content of HIV-1 RNA by polymerase chain reaction; immune status assessment (indicators of the absolute and relative counts of lymphocytes, T-helpers with the $CD3^+CD4^+$ phenotype, T-cytotoxic cells with the $CD3^+CD8^+$ phenotype, the CD4/CD8 immunoregulatory index, and eosinophil and basophil counts).

A total of 1020 cases of HIV infection were analyzed, of which 121 cases with identified allergic pathology were selected. During the study, patients were distributed into groups depending on their viral load. Thus, group 1 (n = 35) included patients with a detectable (>250 copies/ml) viral load and group 2 (n = 86) included patients with HIV infection without a detectable viral load (<250 copies/ml). The distribution of the participants according to gender and age criteria was not performed.

Table 1. Distribution of participants depending on the level of viral load and the presence of drug allergies.

Group	Patients with a history of drug allergy, n	Patients without a history of drug allergy, n	Total
1 (viral load > 250 copies/ml)	14	21	35
2 (viral load < 250 copies/ml)	56	30	86
Total	51	70	121

Table 2. Immune status indicators in the study groups based on the presence of drug allergy.

Group	M ± m							
	Viral load, copies/ml	$CD3^+$, %	$CD3^+CD4^+$, %	$CD3^+CD8^+$, %	CD4/CD8, %	Eosinophils, %	Basophils, %	Lymphocytes, %
1 (n = 61)	70 885.36 ± 44 031.83	78.3 ± 1.1	27.5 ± 1.4	47.2 ± 2.1	2.2 ± 1.5	5.3 ± 1.9	0.5 ± 0.1	34.3 ± 1.3
2 (n = 35)	6120.3 ± 3335.1	78.1 ± 2.4	26.8 ± 2.1	51.6 ± 2.6	0.7 ± 0.1	2.9 ± 0.4	0.5 ± 0.2	32.4 ± 1.9
p	0.15	0.96	0.78	0.18	0.31	0.21	0.98	0.4

Note: group 1: patients with drug allergies; group 2: patients without drug allergy; $CD3^+$: count of $CD3^+$ cells (T-lymphocytes); $CD3^+CD4^+$: count of T-helpers; $CD3^+CD8^+$: count of T-cytotoxic lymphocytes; CD4/CD8: immunoregulatory index.

During the statistical processing of the obtained data in the study, the Student's test (*t*) was used to assess the statistically significant differences in the mean values of the studied indicators of the immune status. The Pearson χ^2 test was used to assess the statistical significance of the differences in allergic manifestations in patients with HIV infection to identify the statistically significant differences between patients with HIV infection with and without drug allergic reactions in terms of the presence or absence of a detectable viral load.

Results and discussion. The initial selection considered 1,020 registered cases of HIV infection among Veliky Novgorod and the Novgorod region residents. The data of the Center's primary documentation from 2000 to 2021 was considered. Information about aggravated allergic anamnesis was revealed in 121 cases. Thus, allergic diseases among patients with positive HIV during the study period were registered in the Novgorod region in 12% of cases.

The further analysis considered the allergic disease etiology, viral load (the number of RNA copies in 1 ml of blood plasma), and data on the patient's immune status (indicators of the levels of lymphocytes $CD3^+$, $CD3^+CD4^+$, $CD3^+CD8^+$, CD4/CD8 index, total number of lymphocytes, eosinophils, and basophils). According to the viral load, two groups of patients were identified, namely those with a viral load of >250 copies/ml (detectable viral load) and those <250 copies/ml (undetectable viral load).

Allergic diseases in the participants were represented by various etiologies, namely pollen (5.7%), household (5.7%), food (19%), chemical (1.9%), drug (59%), and unspecified (6.7%). The most common registered clinical manifestations were dermatitis, urticaria, papular eruption, toxicoderma, rhinitis, and atopic bronchial asthma. Severe allergic reactions were recorded to some drugs (mainly antibacterial drugs, non-steroidal anti-inflammatory drugs, and drugs for local anesthesia), namely angioneurotic edema, asthma attacks, and loss of consciousness, which was recorded in the primary documentation (form No. 025-4/u).

Two groups were formed from the number of patients with HIV infection with recorded cases of allergic reactions (Table 1). Group 1 (n = 35) included data from patients with a history of allergic manifestations and a high viral load according to quantitative polymerase chain reaction (>250 copies/ml). Group 2 (n = 86) included patients with a history of allergic reactions and undetectable viral load (<250 copies/ml). Sample data analysis using the Pearson's χ^2 criterion based on the presence in the history of participants of allergic reactions to drugs (drug allergy) revealed a statistically significant ($p < 0.012$) difference between the groups.

Allergic reactions to antibiotics (45%), antihistamines (4.8%), local anesthetics (50%), and antiretroviral therapy drugs (8%) among the participants with drug allergies were recorded. In the range of antiretroviral therapy drugs, hypersensitivity reactions were induced by groups of nucleoside reverse transcriptase inhibitors (lamivudine/abacavir), non-nucleoside reverse transcriptase inhibitors (efavirenz/nevirapine), and protease inhibitors (lopinavir/ritonavir).

The immune status indicators of patients were also studied (Table 2). In the groups selected, no statistically significant (Student's *t*-test) changes

Table 3. Immune status indicators in the study groups are based on the presence of drug allergy and the level of viral load (VL).

Group	M ± m						
	$CD3^+$, %	$CD3^+CD4^+$, %	$CD3^+CD8^+$, %	CD4/CD8, %	Eosinophils, %	Basophils, %	Lymphocytes, %
1, VL > 250 copies/ml (n = 12)	83.8 ± 1.8	26.2 ± 3.2	53.9 ± 3.7	0.5 ± 0.1	3.8 ± 1.7	0.7 ± 0.3	32.7 ± 2.4
2, VL > 250 copies/ml (n = 49)	76.9 ± 1.3	27.8 ± 1.5	45.5 ± 2.4	2.6 ± 1.8	5.7 ± 2.3	0.5 ± 0.1	34.7 ± 1.5
p	0.003	0.64	0.06	0.26	0.48	0.48	0.48

Note: $CD3^+$: count of $CD3^+$ cells (T-lymphocytes); $CD3^+CD4^+$: count of T-helpers; $CD3^+CD8^+$: count of T-cytotoxic lymphocytes; CD4/CD8: immunoregulatory index.

in the immune status indicators were revealed ($p > 0.05$ in all cases). Therefore, no specific markers determined the predisposition to the development of drug allergic reactions can be concluded among the studied immune status indicators in patients with HIV infection having drug allergies.

Further data analysis of patients with drug allergies and different levels of viral load (Table 3) revealed statistically significant results. Thus, the level of $CD3^+$ cells (T-lymphocytes) was significantly higher in patients with drug allergy and detectable viral load than in patients with drug allergy and undetectable viral load (M ± m values: 83.75 ± 1.81 and 76.89 ± 1.25%, respectively, $p < 0.003$). This phenomenon may be associated with the predominance of the cellular component of immunity over the humoral component in patients with drug allergies. This aspect requires further study using molecular genetic and immunogenetic methods.

The study of allergic reactions in patients with HIV infection is of great clinical importance. Understanding the mechanisms of the development of allergies in combination with HIV infection will contribute to the improvement of the analysis of drug therapy and existing therapeutic methods. Effective therapy must be created considering the characteristics of immunological indicators, namely a decreased level of $CD4^+$ lymphocytes, increased $CD8^+$ lymphocytes, and lymphocytosis. Understanding the cross-reactions can help avoid hypersensitivity reactions in patients with HIV who take antiretroviral drugs.

CONCLUSIONS

1. The most common form of allergy in patients with HIV infection is drug allergy. The most severe manifestations of allergic reactions are also associated with it.

2. The study revealed no possible immune status markers in patients with a burdened allergic history among those studied, which would assess the risk of drug allergy. Concurrently, the prevalence of cellular immunity in terms of the count of $CD3^+$ cells was determined in patients with HIV infection with drug allergy ($p < 0.003$).

3. Further studies using molecular genetic, immunogenetic, and other methods are required to identify the markers of allergic reaction development in patients with HIV infection.

Author contributions. S.A.N. performed the analysis of the obtained data, structuring the information, and typed the text; G.S.A. was the work supervisor; E.I.A. and N.N.N collected and processed the patient data; S.V.B. performed the statistical analysis, and edited the test.

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